Synthesis of (6E)-1-(1-Benzyl-3-Methyl-1H - Pyrazole-5 (4H) Ylidene) Hydrazine Derivatives

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Abstract: **Heterocyclic bearing Nitrogen and Sulphur atoms constitute the core structure of a number of biologically interesting compounds. pyrazole derivatives are well established in the literature as important biologically active heterocyclic compounds[7] these derivatives are the subject of many research studies due to their wide spread potential biological activities. A number of pyrozole-Hydrazine derivatives are used for the treatment of chronic inflammatory diseases including rheumatoid arthritis and multiple sclerosis.**

Keywords: **Pyrazoles; pyrazolone; methyl; Hydrazene; ylidene**

I. INTRODUCTION

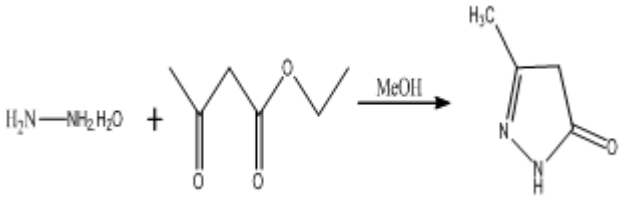
Pyrazoles are the present target of numerous methods, because of their commonness in temporary or moveable flatform in drug discovery programs and in synthesis of biologically active compounds and their reactions in different chemical species This pyrazole ring is the core in various leading drugs such as Viagra, celebrex etc. Pyrazoles are the building blocks for various research programs in pharmaceutical and agricultural fields Alfa Aesar is the source of various pyrazoles derivatives Already many of the pyrazoles derivatives are clearly notified in various literatures, here are just a few examples of their use. Numerous patents describe the use of the 3-aminopyrazole analogue (H30935) as building block to more complex moieties, such as potential drug candidates. 5-Aminopyrazoles such as H32831 have been used in heterocyclizations involving Narylmaleimides or ethyl2-thien-3-yl-3-hydroxypropenoate. Studies involving H32918 as a building block showed that 3-aminopyrazole derivatives can be selected based MK2-inhibitors. Suzuki coupling of a 7-bromo-1,4-benzoxazine derivative with pyrazole boronate esters (such as H32930, H53139 and L19654) lead to a series of pharmacological active molecules, as potential PI3 kinase inhibitors for the treatment of chronic inflammatory diseases including multiple sclerosis and rheumatoid arthritis.

II. PRESENT WORK

Scheme 1.

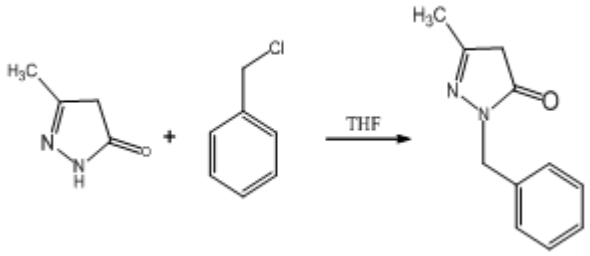
Step 1. Preparation of 3- methyl 5-hydroxy pyrazolone.

Take 6.33 ml of ethyl acetate in 250 ml beaker. To this added 3.5 ml of hydrazine hydrate. A white solid is obtained. To this added 4 ml of methanol. Then stir the reaction mixture for 40 min at room temperature. Cool the reaction mixture & filtered. A white crystalline solid is obtained,melting point is 176^0c

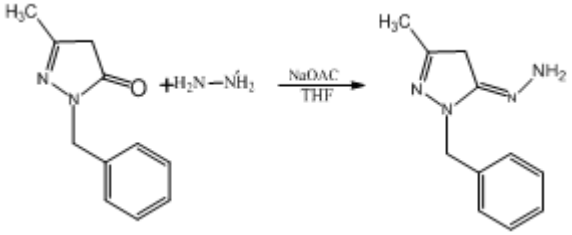


Step 2. Preparation of 1- benzyl 3-methyl-5-pyrazolone.

Take 1 eq of 3-methyl 5-hydroxy pyrazole in a round bottom flask. To this 1.2 eq of benzyl chloride was added. Add 10ml of THF to this mixture. Reflux the reaction mixture for 5 hrs. Check TLC for every 1hr, Melting Point at 218^0



Step 3.Preparation of (6E)-1-(1-benzyl-3-methyl-1H-pyrazole-5(4H) ylidene) hydrazine.



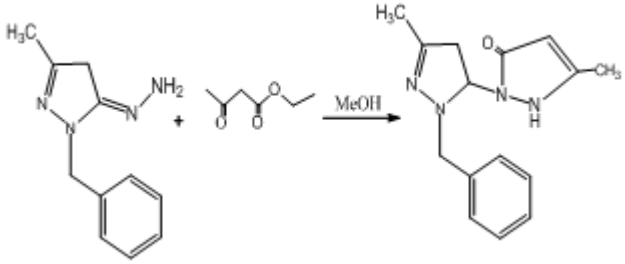
Compound	*Mol. wt*	*Equivalents*	*M. moles*	*Wt (Or) Volume*	*Density*
1-Benzyl-3-methyl-5-pyrazolone	188	1	1.595	0.3 gr	
Hydrazine Hydrate	50	1.2	1.814	0.2616 gr	

Methanol	32	1.2	9.6	9.280 ml	1.131

Take 1 eq of 1- benzyl 3-methyl 5-pyrazolone in a round bottom flask[8]. To this add 1.2 eq of hydrazine hydrate & 1.2 eq Methanol as a solvent then add one pellet of NaOH to the reaction mixture. Reflux the reaction mixture & checked the TLC for every 1h melting Point 193^{0}C.

Step 4.2-(1-benzyl-4,5-dihydro-3-methyl-1H-pyrazol-5-yl)-2,3-dihydro-6-methylpyridazin-4(1H)-one.

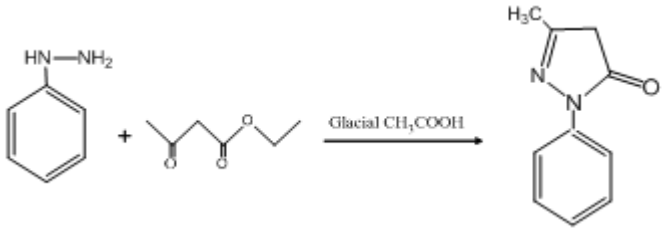
Take 1 eq above compound in a round bottom flask and to it add 1.2 eq of Ethyl aceto acetate and then add 10ml of Methanol and reflexed it. And for every 1h TLC is checked. % yield of compound: 56%, Melting point:148^{0}C



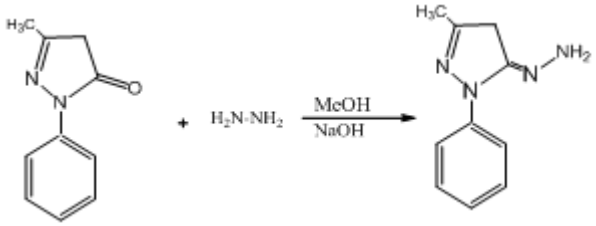
Scheme:2

Step5: Preparation of 1-phenyl 3-methy5-pyrazolone.

Take 1 eq of Phenyl hydrazine and 1.5 eq of Ethyl aceto acetate into a china dish to this added 3-4 drops of acetic acid and heat the mixture on boiling bath for 1h with constant stirred to form yellow colour syrup. Then collect the syrup and added 5ml of Ether stirred as crystalline pyrazolone formed, filter the compound then washed with Ether 2-3 times, then recrystallize the product from Methanol, the colourless crystal is formed.



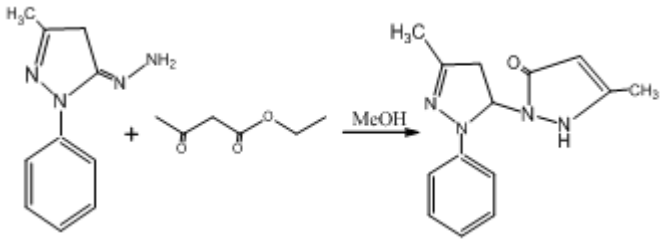
Step 6: 1-(1-benzyl-4,5-dihydro-3-methyl-1H-pyrazol-5(4H)-yidene)-5 Hydrazene



Compound	*Mol. Wt*	*Equivalents*	*m. moles*	*Wt (Or) Volume*	*Density*
Atipyrin	174	1	1.5957	0.3 gm	
Hydrazene hydride	50	1.2	1.814	0.2616 gm	
Methanol	32	1.2	9.6	9.280 ml	1.131

Take 1 eq of antipyrine in a 250 ml RB to this added 1.2 eq of hydrazine hydrate and to this reaction mixture added 8 ml of Methanol as a solvent and refluxed the mixture for about 6 – 8 h and checked the TLC for every one 1 h Melting Point 186^{0}C.

Step7:2,3-dihydro-2-(4,5 dihydro-3methyl-1-phenyl-1H-pyrazol-5-yl)-6-methyl pyridazin-4(1H)- one.



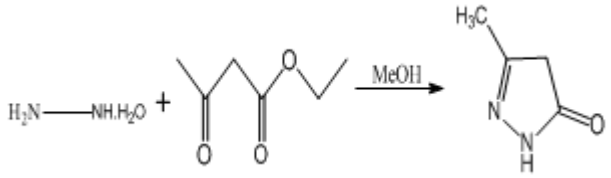
Compound	**Mol. Wt**	**Equivalents**	**m.moles**	**Wt (Or) Volume**	**Density**
(1-benzyl-4,5-dihydro-3-methyl-1H-pyrezole-5(4H)-ylidene) 5-hydrazin	202	1	1.5957	0.3 gm	
Ehtyl aceto acetate	130	1.2	1.814	0.2616 gm	
Methanol	32	1.2	9.6	9.280 ml	1.131

In to a round bottomed flask taken 1 eq. Wt. Of above compound and then added 10. Ml of CH_3OH and 1.2 eq. Of ethyl aceto acetate. To this reaction mixture 1 drop of dihydrosulphuric acid is also added and then the reaction mixture is refluxed for 8-10 hours and checked the TLC for every One hour. The % yield of the compound is 64.74(the reaction was proceeded up to step -6 and there is no cyclization taken in step -7.

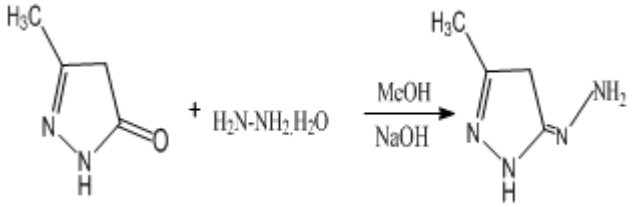
Scheme 3.

Step 8. Preparation of 3-methyl 5 -hydroxy pyrazolone

Into a 250 ml beaker , taken 6.33ml of ethyl aceto acetate. Into the same beaker added 3.5 ml of hydrazine hydrate . A white solid is noticed . 4 ml of CH_3OH was added to this beaker . Then the reaction mixture was stirred for 40 mins .Then it is cooled and filtered . Acrystaline solid which is white colour is obtained . The M.P of this crystalline solid is 176^{0}C



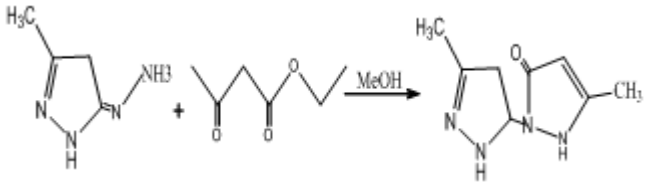
Step 9: Preparation of 3-methyl-1H-pyrazole-5-hydrazene.



Compound	Mol. Wt	Equivalents	m.moles	Wt (Or) Volume	Density
3-methyl-1-hydro 5-pyrazolone	96	1	1.5957	0.3 gm	
Hydrazene Hydride	50	1.2	1.814	0.2616 gm	
Methanol	32	1.2	9.6	9.280 ml	1.131

Taken 1 eq of 3-methyl-1-hydro pyrazone in around bottom flask and they added 1.2 eq of Hydrazene Hydrate and then added a 10ml Methanol to it as solvent and then these reaction mixture is reflux 4-5h and every 1 h TLC was checked. Melting Point is 235^0C.

Step 10: 2,3-dihydro-2-(4,5-dihydro-3-methyl-1-phenyl-1H-pyrazol-5-yl)-6-methyl pyridazin-4(1H)-one



Take 1 eq of above compound in to a clean round bottom flask and added to this 1.2 eq of Ethyl aceto acetate and the reaction mixture added 10 ml of Methanol as a solvent and refluxed 4 h and for every 1h TLC was checked. % yield of compound:68%(up to step 9 there is no cyclisation is takes place in step 10).

III. CONCLUSIONS

The Compounds prepared are

1. Synthesis of 1-(1-4,5-dihydro-3-methyl-1H-pyrazole-5-yl)-5-methyl pyrazolidin-3-one.
2. Synthesis of 1-(1-benzyl-4,5-dihydro-3-methyl-1H-pyrezole-5(4H)-ylidene)5-methyl Pyrazolidin-3-one.
3. Synthesis of 1-(1-4,5-dihydro-3-methyl-1H-pyrazole-5-yl) 5-methyl pyrazolidin-3-one.

These derivatives are biologically active so the above synthesized Compounds may exhibit biologically activeness.

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